Heritability of Perinatal Depression and Genetic Overlap with Non-perinatal Depression

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I, as the corresponding author, affirm that I had access to all data from the study, both reported and unreported. I also affirm that I had complete freedom to direct the analysis and reporting, without influence from the sponsors. I also affirm that all listed authors have contributed to the study according to the three conditions listed in the "Guidelines for Authors on Preparing Manuscripts", and that all authors agree to submission and copyright transfer.

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ABSTRACT

Objective: To investigate the relative importance of genetic and environmental influences on perinatal depression, and the genetic overlap between perinatal depression and non-perinatal depression.

Method: Analyses were conducted using structural equation modeling for (1) a validated self-rated screening tool for perinatal depression, the lifetime version of the Edinburgh Postnatal Depression Scale, in 3,427 Swedish female twins, and (2) clinical diagnoses of depression separated into perinatal depression and non-perinatal depression in a Swedish population-based cohort of 580,006 sisters.

Results: In the twin study, the heritability of perinatal depression was estimated at 54% (95% CI, 35-70%) with the remaining variance attributable to non-shared environment (46%; 95% CI, 31-65%). In the sibling design, the heritability of perinatal depression was estimated at 44% (95% CI, 35-52%), and the heritability of non-perinatal depression at 32% (95% CI, 24-41%). Bivariate analysis showed that 14% of the total variance (or 33% of the genetic variance) in perinatal depression was unique for perinatal depression.

Conclusions: The heritability estimate is higher for perinatal depression than for non-perinatal depression. Further, a third of the genetic contribution is unique to perinatal depression and not shared with non-perinatal depression, suggesting only partially overlapping genetic etiologies for perinatal depression and non-perinatal depression. We suggest that perinatal depression constitutes a more homogenous subset of depression that could be prioritized for genomic discovery efforts. Further, these findings have direct

translational impact that can assist clinicians in the counsel of their patients regarding risk and prognosis of perinatal depression.

INTRODUCTION

Perinatal depression, defined as depressive illness occurring during pregnancy (antenatal depression) or following childbirth (postpartum depression), impacts at least 10-15% of women, and confers substantial morbidity, mortality, and personal and societal costs.(1-4) The clinical presentation of perinatal depression features low mood, anxiety, rumination, and in severe cases suicidal or infanticidal ideation.(5) Historically, perinatal depression has been conspicuously under-studied as compared to major depressive disorder.(6)

Major depressive disorder is defined as marked and persistent depressed mood associated with physical and cognitive signs and symptoms.(7) Depression is common, costly, and is projected to be the second leading cause of disability worldwide by 2020.(8-11) The heritability of major depressive disorder has been estimated at 31–42%.(12,13) In contrast to other major psychiatric disorders, discerning the genetic basis of depression has proven to be more challenging. Genome-wide linkage studies, candidate gene studies, and genome-wide association studies have not been successful in identifying risk loci that meet contemporary standards for replication.(14) The relatively modest heritability of depression, as compared to other major psychiatric disorders, may be one reason for the substantially lower yield of identified genetic loci.(15) Another reason is that depression is a markedly heterogeneous disorder.

In contrast, perinatal depression may represent a more homogenous disorder. Perinatal depression occurs in women of reproductive age and is coupled to pregnancy and childbirth. The limited literature on the genetic basis of perinatal depression suggests a heritable component that may be greater than in major depressive disorder.(16-18) There are two small studies showing clustering in families.(17,18) Murphy-Eberenz et al.

reported odds ratios for prediction of sibling status for perinatal depression or postpartum depression between 2.28-3.96.(17) Forty et al. studied female siblings and described familiality for postpartum depression maximized with a postpartum onset definition of 6–8 weeks following childbirth (tetrachoric correlation coefficient=0.62, 95% CI=0.16-0.88; p=0.01) in women with recurrent depression.(18) Finally, an Australian study of 1,676 twins estimated heritability of lifetime postpartum depression at 25%.(16)

Some have argued that perinatal depression is partly or wholly distinct from major depressive disorder. According to this view, the biological underpinnings of perinatal depression differ from those in non-perinatal depression in that sensitivity to the dramatic fluctuations in gonadal hormone serum concentrations during the perinatal period probably play a pathogenic role.(19,20) This implies that perinatal depression and non-perinatal depression are at least partially different disorders where perinatal depression features distinctive genetic and environmental etiological risk factors. The alternative viewpoint is that perinatal depression is merely an episode of major depressive disorder occurring in the temporal period beginning during pregnancy or the immediate postpartum. Given the uncertainty about the degree to which perinatal depression and non-perinatal depression are distinct and the limited literature on the genetic basis of depression during the perinatal period, there is a great need for improved understanding of the genetic basis of perinatal depression, and the extent to which perinatal depression and non-perinatal depression overlap genetically. In this study, we used data from a validated screening tool for perinatal depression in 3,427 twins from the Swedish Twin Registry to estimate the relative contributions of genetic (heritability) and environmental risk factors to the liability to perinatal depression in a classical twin design. We then used Swedish population data from over 580,000 sisters and national treatment registers to estimate the heritability of perinatal depression, the heritability of non-perinatal

depression, and the genetic and environmental overlap between the two.

METHODS

Classical twin study

Study population. The Swedish Twin Registry contains almost 200,000 Swedish twins born between 1886-2008.(21) The sub-study "Screening Across the Lifespan Twin study: the Younger" (SALTY) was conducted between 2009-2010 and included 11,372 twins from the Swedish Twin Registry with a median birth year of 1950 (54.3% female). The SALTY study included an extensive self-report questionnaire that covered many different areas, including perinatal depression.(22) The sample consisted of females from the SALTY study who reported having given birth to a living child, and who completed the lifetime Edinburgh Postnatal Depression Scale. This included 3,427 individual twins (1,516 female monozygotic and 1,911 female same-sex dizygotic twins) and both members of 1,106 twin pairs. Zygosity was determined using DNA for 27% of the twin females. For the remainder, zygosity was assigned based on questions about intra-pair physical similarities in childhood.(21)

Perinatal depression classification. We assessed onset of mood symptoms both during pregnancy and postpartum using a retrospective lifetime version of the Edinburgh Postnatal Depression Scale, previously described in detail.(23) The Edinburgh Postnatal Depression Scale is the most widely used patient-rated assessment instrument for perinatal depressive illness in the world and has demonstrated good sensitivity and specificity in both antenatal and postpartum depression.(2,24) The lifetime version of the Edinburgh Postnatal Depression Scale includes the same 10 items used in the original scale, but was modified to assess previously experienced (or lifetime) perinatal depression.(23) A score of ≥12 on the scale is the accepted standard cut-off to identify

depressive illness and has been widely used in the literature, and was used in this study to define a binary outcome.(24,25)

Statistical analysis. The classical twin methodology relies on the different relatedness between monozygotic and dizygotic twins. Monozygotic twins are considered genetically identical whereas dizygotic twins share an average of 50% of their segregating alleles. If genes influence a trait, there will be more pronounced twin similarity within monozygotic than within dizygotic pairs. By modeling twin covariance structures in monozygotic and dizygotic pairs, the variation in a phenotype is decomposed into additive genetic (A), shared environmental (C), and non-shared environmental (E) factors.(26) We used a liability-threshold approach, assuming that the observed binary variable came from an underlying continuous liability of the trait.(26) A threshold was assumed, where a 1 was assigned if an individual had a liability greater than the threshold, and 0 otherwise. The distribution of underlying liabilities were assumed normal, and the correlations between these underlying normal distributions could be estimated.(27) The resulting tetrachoric correlations form the basis of the heritability analysis. Note that the key assumptions of normally distributed liability and equal-environments have strong empirical support.(28)

Sibling design

Study population. To evaluate genetic and environmental influences on perinatal depression and non-perinatal depression in a larger and more generalizable setting, we included a population-based cohort from Swedish national register data. We used the Swedish personal identification numbers to link national Swedish longitudinal registries with high accuracy. The Swedish Medical Birth Register covers 99% of all births since 1973,(29) and was linked to the Multi-Generation Register that contains information of first-degree relatives for persons born 1932 and later.(30) The Medical Birth Register and

Multi-Generation Register were linked to the Swedish Twin Registry to obtain information on twins and their zygosity. All parous women who had given birth to their first child after 1973 were included. Further, the women had to be born in Sweden, could not have emigrated and moved back to Sweden more than once, and had to have at least one sister fulfilling the same criteria. Due to the low observed occurrence of perinatal depression in the registers (0.6%; Table 2), we opted for a design that included up to four full or half-siblings per nuclear family, covering 99.8% of the eligible population. We identified a total of 580,006 parous female siblings from 260,384 unique families. This allowed for comparisons in 313,632 full-sister pairs, 28,568 maternal half-sister pairs, 33,931 paternal half-sister pairs, 2,104 dizygotic twin sister pairs, and 2,225 monozygotic twin sister pairs. A total of 1,572 twin sisters overlapped between the two different designs.

Disease classification. We linked all subjects in the study population to the Swedish National Patient Register, containing all Swedish psychiatric inpatient admissions since 1973, and psychiatric specialist outpatient treatment contacts since 2001.(31) The register contains admission dates along with the main discharge diagnosis code, and up to eight secondary diagnosis codes in accordance with the International Classification of Disease (ICD). Treatment contacts for depression were defined using diagnostic codes: ICD-8 296.00, 296.40, 296.41, 790.20; ICD-9 296.2, 296.3, 296.9, 298.0, 300.4, 309.0, 309.1, and 311; or ICD-10 F32.0, F32.1, F32.2, F32.3, F32.8, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, F33.8, F33.9, F34.1, and F41.2. These diagnostic codes were selected to capture as many women with perinatal depressive symptoms as possible. The perinatal period was defined as any point from estimated date of conception through six-months postpartum. Although the onset of postpartum depression is often within 4-6 weeks of childbirth,(7) we have intentionally expanded our definition to include women seeking care up to six

months postpartum, as treatment onset may be substantially delayed from symptom onset. Many women delay seeking treatment due to concerns of stigma of mental health treatment,(32) uncertainty about the nature of symptoms (postpartum "blues" or a normal transition to motherhood versus an illness state requiring treatment), or perceived lack of time for self-care.(33)

The conception date was calculated using the birthdate of the child and gestational age at delivery. Perinatal depression was defined as ≥1 inpatient or outpatient treatment contact for unipolar depression within a perinatal period. Non-perinatal depression was defined as unipolar depression at any other time in a woman's life.

The perinatal period was further separated into an antenatal and a postnatal period to allow heritability estimation of antenatal and postnatal depression respectively. For this purpose, the postnatal period was extended to 12 months.

Statistical analysis. To estimate the relative importance of genetic and environmental effects, we considered up to four female siblings simultaneously in family clusters. The family clusters included siblings who shared at least one parent, allowing full and half-siblings within a family. No individual was included in more than one cluster and no known sibling relations existed between clusters. If half siblings were clustered into more than one family, only the largest family was included to avoid duplicate entries. If a family cluster consisted of more than four individuals, four individuals were randomly selected.

As in the classical twin design, monozygotic and dizygotic twins were assumed to share 100% and 50% of their additive genetic factors, A; the corresponding values were 50% for full siblings, and 25% for maternal and paternal half siblings. The shared environment, C, was modeled to be fully shared by all sibling types except paternal half

siblings were it was assumed unshared as Swedish half siblings are much more likely to live with their mother.(34) Individual specific environment (E) was modeled to be unique to each individual. Relying on these assumptions we could determine the expected correlation structures for each specific type of family cluster depending on the sibling types were included. We again used the liability-threshold approach for analysis of the binary traits. We fitted univariate models where the variance in each disease separately were modeled to be due to A, C, and E. We then fit bivariate models where the variance and covariance in each trait were simultaneously modeled to be due to A, C, and E. To estimate how much of the variance in perinatal depression that could be attributed to A, C, and E in common with non-perinatal depression and A, C, and E unique to perinatal depression we used a Cholesky decomposition approach.(26) As this was modeled in a regression framework, we adjusted the prevalences for whether the family included half-siblings as well as for birth year (both linear and squared). Non-perinatal depression was additionally adjusted for time at risk (linear and squared) and perinatal depression for number of offspring.

Statistical software

Data were prepared using SAS v9.3. Analyses were performed using the OpenMx package in R 3.0.2. In the twin-only analysis, missing values were handled by full information maximum likelihood. No missing values existed for the diseases and covariates in the sibling analyses.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethical approval

The study was approved by the regional ethics committee in Stockholm.

RESULTS

Classical twin design

The observed occurrence of perinatal depression in the twin sample (lifetime Edinburgh Postnatal Depression Scale total score ≥12) was 7.6% (Table 1). In the ACE model, there was no significant common environmental effect, and therefore we fitted a model where C-parameter was fixed at zero (AE model) that did not fit the data significantly worse (χ^2=0.00, degrees of freedom=1, p-value=1.00). The heritability of perinatal depression based on the lifetime Edinburgh Postnatal Depression Scale was estimated at 54% (95% CI, 35-70%) with the remaining variance due to non-shared environment (46%) (Table 1).

Sibling design

Based on treatment contacts, the observed occurrence of perinatal depression was 0.6% (Table 2). The heritability of perinatal depression was estimated at 44% (95% CI, 35-52%), with the remaining variance attributable to non-shared environment (Table 2). The heritability of non-perinatal depression was estimated at 32% (95% CI, 24-41%), with the remaining variance attributable to shared environment (6%), and non-shared environment (62%) (Table 2).

In a bivariate model all C-parameters, except C-unique for non-perinatal depression, was estimated close to zero. Therefore, we fitted an AE model where these parameters were set to zero, and the model fit did not deteriorate (χ^2=0.53, degrees of freedom=2, p-value=0.77). The bivariate analysis revealed that 14% of the total variance (or 33% of the

genetic variance) in perinatal depression was unique for perinatal depression and not in common with non-perinatal depression (Table 3 and Figure 1).

The heritability of antenatal depression was estimated at 37% (95% CI, 27-47%), with the remaining variance attributable to non-shared environment, while the heritability of postnatal depression was estimated at 40% (95% CI, 31-49%) with the remaining variance attributable to non-shared environment (Table 4).

DISCUSSION

This is the largest and most comprehensive genetic epidemiological study of perinatal depression yet reported. Using Swedish national cohorts, we estimated the heritability of perinatal depression with two different approaches. Our classical twin design estimated the univariate heritability of perinatal depression at 54% (95% CI, 35-70%) and the sibling study estimated it at 44% (95% CI, 35-52%). Despite the marked difference in observed occurrence of perinatal depression in the two designs (0.6% and 7.6%), the heritability estimates are similar and the confidence intervals overlap, which suggests that both approaches capture the same underlying liability for perinatal depression. The different observed occurrence rates are likely explained by the different methodologies; self-report in the twin design, and register based treatment contacts in the sibling design. Thus, the sibling design did not account for women who did not seek treatment for perinatal depression but who would endorse symptoms on a self-report questionnaire.(35)

To our knowledge, there has only been one previous heritability study of depression around pregnancy.(16) This Australian twin-study (N=1,676) estimated the heritability of lifetime postnatal depression at 25% (95% CI, 13-42%). Our estimates for lifetime perinatal depression at 54% (95% CI, 35-70%) in the twin design and at 44% (95% CI,

35-52%) in the sibling design, indicate a larger genetic contribution than in the Australian study.

Division of the perinatal period allowed estimating the heritability of antenatal depression at 37% (95% CI, 27-47%) and postnatal depression at 40% (95% CI, 31-49%) (Table4). The variance of both antenatal and postnatal depression displayed a similar pattern as the variance of perinatal depression as a whole with variance explained by additive genetics of similar size and non-shared environment only, without contribution of shared environment.

We estimated the heritability of non-perinatal depression at 32% (95% CI, 24-41%), which is slightly lower than previous estimates of major depressive disorder.(13) However, we only included parous women, and separated the perinatal and non-perinatal depressive episodes.

In a bivariate heritability analysis of perinatal depression and non-perinatal depression, 14% of the variance in perinatal depression was explained by genetic factors unique for perinatal depression and 28% by genetic factors shared with non-perinatal depression. In other words, of the total genetic variation for perinatal depression, 2/3 is shared with non-perinatal depression and 1/3 is unique for perinatal depression.

The heritability estimates of perinatal depression in these two analyses may have particularly important implication. A critical issue in genetic research in unipolar mood disorders is etiological heterogeneity. It is likely that there are multiple “types” of persistent depressive disorders. Considering these disorders as a single entity may effectively combine different sets of genetic and environmental etiological processes resulting in higher prevalence and lower heritability.(36-38) This combination is arguably unfavorable for genomic discovery efforts.(39)

Thus, we hypothesize that perinatal depression represents a form of unipolar mood disorder that could be prioritized for genomic discovery efforts. In effect, we suggest a "divide and conqueror" approach to understanding the genomics of unipolar mood disorders. Appropriately powered studies of perinatal depression could deliver genomic findings important to disentangling its etiology as well as of potential relevance to major depressive disorder. We note that women with perinatal depression are readily ascertained clinically enabling efficient accrual of large samples. Ultimately, improved identification of women at risk for perinatal depression could lead to targeted interventions to prevent, identify, and more effectively treat perinatal depression in order to minimize adverse sequelae for mother and child.

The current study has several strengths. The study uses both classical twin and sibling designs. Two designs with different tools to measure perinatal depression; the validated Edinburgh Postnatal Depression Scale in 3,427 female twins, and treatment contacts from national Swedish registers in over 580,000 sisters that allowed for separation of depressive illness into perinatal depression and non-perinatal depression, and perinatal depression further into antenatal and postnatal depression. Additionally, sensitivity analyses suggested that the unique genetic component seen in perinatal depression was not explained by bipolar disorder or schizophrenia (see Supplement SA1), and that the unique genetic component was linked to the actual pregnancy (see Supplement SA2).

This study also has limitations. The Swedish National Patient Register does not include outpatient admissions before 2001 and no primary care data. The percentage of women being treated for depression exclusively by the primary care in Sweden is not known, but the observed occurrence of perinatal depression based on treatment contacts is likely an underestimation of the true prevalence. Further, depression identified using the National Patient Register will likely be on the more severe end of the spectrum than depression

identified using the Edinburgh Postnatal Depression Scale. If the assumption of an underlying continuous liability in the threshold model is true this should not affect the heritability estimates. Indeed, increasing or decreasing the Edinburgh Postnatal Depression Scale cut-off to capture more or less severe depressive illness did not change the heritability estimates (see Supplement SA3). The observed outcome occurrence of perinatal depression among the twins using the Edinburgh Postnatal Depression Scale was 7.6%, which is lower than observed in other studies (10-15%).(1-4) This could be due to the participants being exclusively twins and the retrospective assessment, rather than being assessed at a maternal healthcare unit. When estimating the heritability of antenatal and postnatal depression respectively, the postnatal period had to be expanded to 12 months to include enough cases to allow estimation. While this deviates from the definition of perinatal depression that includes a six-month postnatal period, analysis of perinatal depression using a 12-month postnatal period revealed almost identical results with the heritability estimated at 43% (95% CI, 34-51%) and the remaining variance explained by non-shared environment (57%; 95% CI, 49-66%). We were not able to restrict the postnatal period to the first four or six weeks. However, an early onset depression might not lead to contact with the healthcare within this period and could therefor remain undetected when using treatment contact data. Examination of differences regarding timing of onset of symptoms in pregnancy versus postpartum has been a central issue in recent work,(40) and future research should focus on further elucidating the genetic and biological contributions to the timing of onset of symptoms.

These findings provide important information that will assist clinicians as they counsel their patients regarding the risk and prognosis of perinatal mood disorders. For example, the heritability of a disorder has a direct translational impact in discussions between clinician and patients. Most patients will ask fundamental questions as to “why do I have

perinatal depression?", "was it my fault?", "what's the risk next time?". This study highlights the critical need for clinicians providing obstetrical care to obtain detailed information regarding the patient's personal and family history of psychiatric illness that began in the perinatal period. Integration of genetic risk with environmental influences is vital for the appropriate tailoring of individual treatment and discussions of prognosis.

In conclusion, we report the largest heritability studies of perinatal depression to date, indicating a larger heritability of perinatal depression than that for depression occurring outside of the perinatal period, and the first bivariate heritability study of perinatal and non-perinatal depression, revealing a third of the genetic variance unique for perinatal depression. We believe that perinatal depression represents a form of unipolar mood disorder that can be utilized by clinicians in discussions with their patients and could be prioritized for genomic discovery efforts.

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FIGURES AND TABLES

Table 1. Univariate heritability estimate of perinatal depression using classical twin design (N=3,427)*

Table 2. Univariate heritability estimates of perinatal depression and non-perinatal depression using sibling design (N=580,006)*

Table 3. Estimated variance in perinatal depression

Table 4. Univariate heritability estimates of antenatal depression and postnatal depression using sibling design (N=580,006)*

Figure 1. Estimated variance in perinatal depression*

* Variance accounted for by genetic, shared environmental, and non-shared environmental effects for perinatal depression, either unique for perinatal depression or in common with non-perinatal depression. No variance accounted for by shared environmental effects.

Table 1. Univariate heritability estimate of perinatal depression using classical twin design (N=3,427)*

Model	Outcome Occurrence	Estimated Variance (95% CI)[a]			Tetrachoric Correlation (SE)	
			Environment			
		Additive Genetic (A)	Shared (C)	Non-shared (E)	Monozygotic Twins	Dizygotic Twins
ACE	7.6%	0.54 (0.00-0.70	0.00 (0.00-0.46)	0.46 (0.30-0.66)	0.55 (0.09)	0.22 (0.14)
AE[b]	7.6%	0.54 (0.35-0.70)	NA	0.46 (0.31-0.65)	0.55 (0.09)	0.22 (0.14)

Abbreviations: CI, confidence interval. SE, standard error. NA, not applicable.

* Perinatal depression was defined using the lifetime Edinburgh Postnatal Depression Scale, where a score of ≥12 was used to define a binary outcome. The C component was not significant in the initial ACE model, and an AE model excluding the C component was fitted.

[a] Profile likelihood confidence intervals.

[b] An AE model, were the C parameter was fixed at zero, was considered as the estimate of C was zero in the ACE model.

Table 2. Univariate heritability estimates of perinatal depression and non-perinatal depression using sibling design (N=580,006)*

Disorder	Model	Outcome Occurrence	Estimated Variance (95% CI)[a]		
				Environment	
			Additive Genetic (A)	Shared (C)	Non-shared (E)
Perinatal Depression	ACE	0.6%	0.44 (0.35-0.52)	0.00 (0.00-0.01)	0.56 (0.48-0.64)
Tetrachoric Correlations			**SE**	**Positive concurrent pairs[d]**	
Monozygotic Twins		0.45	(0.15)	2	
Dizygotic Twins[b]		-0.83	(0.18)	0	
Full Siblings		0.23	(0.03)	56	
Maternal Half-siblings		0.01	(0.07)	4	
Paternal Half-siblings		0.05	(0.07)	5	
Perinatal Depression	AE[c]	0.6%	0.44 (0.35-0.52)	NA	0.56 (0.47-0.64)
Tetrachoric Correlations			**SE**	**Positive concurrent pairs[d]**	
Monozygotic Twins		0.45	(0.15)	2	
Dizygotic Twins[b]		-0.83	(0.18)	0	
Full Siblings		0.23	(0.03)	56	
Maternal Half-siblings		0.01	(0.07)	4	
Paternal Half-siblings		0.05	(0.07)	5	
Non-perinatal Depression	ACE	5.4%	0.32 (0.24-0.41)	0.06 (0.02-0.10)	0.62 (0.57-0.66)
Tetrachoric Correlations			**SE**	**Positive concurrent pairs[d]**	
Monozygotic Twins		0.52	(0.06)	31	
Dizygotic Twins		0.15	(0.10)	9	
Full Siblings		0.22	(0.01)	1,834	
Maternal Half-siblings		0.13	(0.02)	296	
Paternal Half-siblings		0.05	(0.02)	239	

Abbreviations: NA, not applicable. CI, confidence interval. SE, standard error.

* Register based data on hospital admissions for depression was used to define perinatal depression and non-perinatal depression (see Methods).

[a] Wald type confidence intervals, standard error calculated using the delta method.

[b] No concordant dizygotic twin pairs for perinatal depression.

[c] An AE model, were the C parameter was fixed at zero, was considered as the estimate of C was zero in the ACE model.

[e] Number of pairs consisting of two individuals positive for the disorder.

Table 3. Estimated variance in perinatal depression

Model	Estimated variance (95% CI)[a]					
			Environment			
	Additive Genetic (A) - unique[b]	Additive Genetic (A) - in common[c]	Shared (C) unique[b]	Shared (C) - in common[c]	Non-shared (E) - unique[b]	Non-shared (E) - in common[c]
ACE	0.16 (0.13-0.18)	0.26 (0.20-0.32)	0.00 (0.00-0.00)	0.00 (0.00-0.01)	0.42 (0.38-0.45)	0.17 (0.14-0.20)
AE[d]	0.14 (0.12-0.16)	0.28 (0.22-0.35)	NA	NA	0.42 (0.38-0.45)	0.16 (0.13-0.19)

Tetrachoric Correlations		SE	Positive concurrent pairs[e]
Monozygotic Twins	0.33	(0.10)	9
Dizygotic Twins	0.05	(0.29)	1
Full Siblings	0.16	(0.01)	381
Maternal Half-siblings	0.08	(0.03)	75
Paternal Half-siblings	0.06	(0.02)	67

Abbreviations: CI, confidence interval. NA, not applicable. SE, standard error.

[a] Wald type confidence intervals, standard error calculated using the delta method.

[b] Variance explained in perinatal depression by component unique for perinatal depression and not in common with non-perinatal depression.

[c] Variance explained in perinatal depression by component in common with non-perinatal depression.

[d] An AE model, were the C parameter was fixed at zero, was considered as the estimate of C was zero in the ACE model (except C unique for non-perinatal depression).

[e] Number of pairs consisting of one individual positive for perinatal depression, and the other positive for non-perinatal depression. Each pair contributes with two combinations; perinatal depression sibling 1 vs. Non-perinatal depression sibling 2, and vice versa.

Table 4. Univariate heritability estimates of antental depression and postnatal depression using sibling design (N=580,006)*

Disorder	Model	Outcome Occurrence	Estimated Variance (95% CI)[a]		
				Environment	
			Additive Genetic (A)	Shared (C)	Non-shared (E)
Antenatal Depression	ACE	0.3%	0.36 (0.27-0.45)	0.02 (-0.04-0.09)	0.62 (0.54-0.70)
Antenatal Depression	AE[b]	0.3%	0.37 (0.27-0.47)	NA	0.62 (0.51-0.73)
Tetrachoric Correlations			**SE**	**concurrent**	
Monozygotic Twins		-0.82	NA[c]	0	
Dizygotic Twins		-0.64	NA[c]	0	
Full Siblings		0.24	(0.00)	18	
Maternal Half-siblings		0.15	(0.17)	2	
Paternal Half-siblings		0.04	(0.11)	2	
Postnatal Depression	ACE	0.4%	0.40 (0.27-0.52)	0.00 (-0.03-0.03)	0.60 (0.49-0.71)
Postnatal Depression	AE[b]	0.4%	0.40 (0.31-0.49)	NA	0.60 (0.51-0.69)
Tetrachoric Correlations			**SE**	**concurrent**	
Monozygotic Twins		0.64	(0.13)	3	
Dizygotic Twins		-0.84	NA[c]	0	
Full Siblings		0.19	(0.00)	33	
Maternal Half-siblings		0.08	(0.07)	6	
Paternal Half-siblings		0.07	(0.09)	3	

Abbreviations: NA, not applicable. CI, confidence interval. SE, standard error.

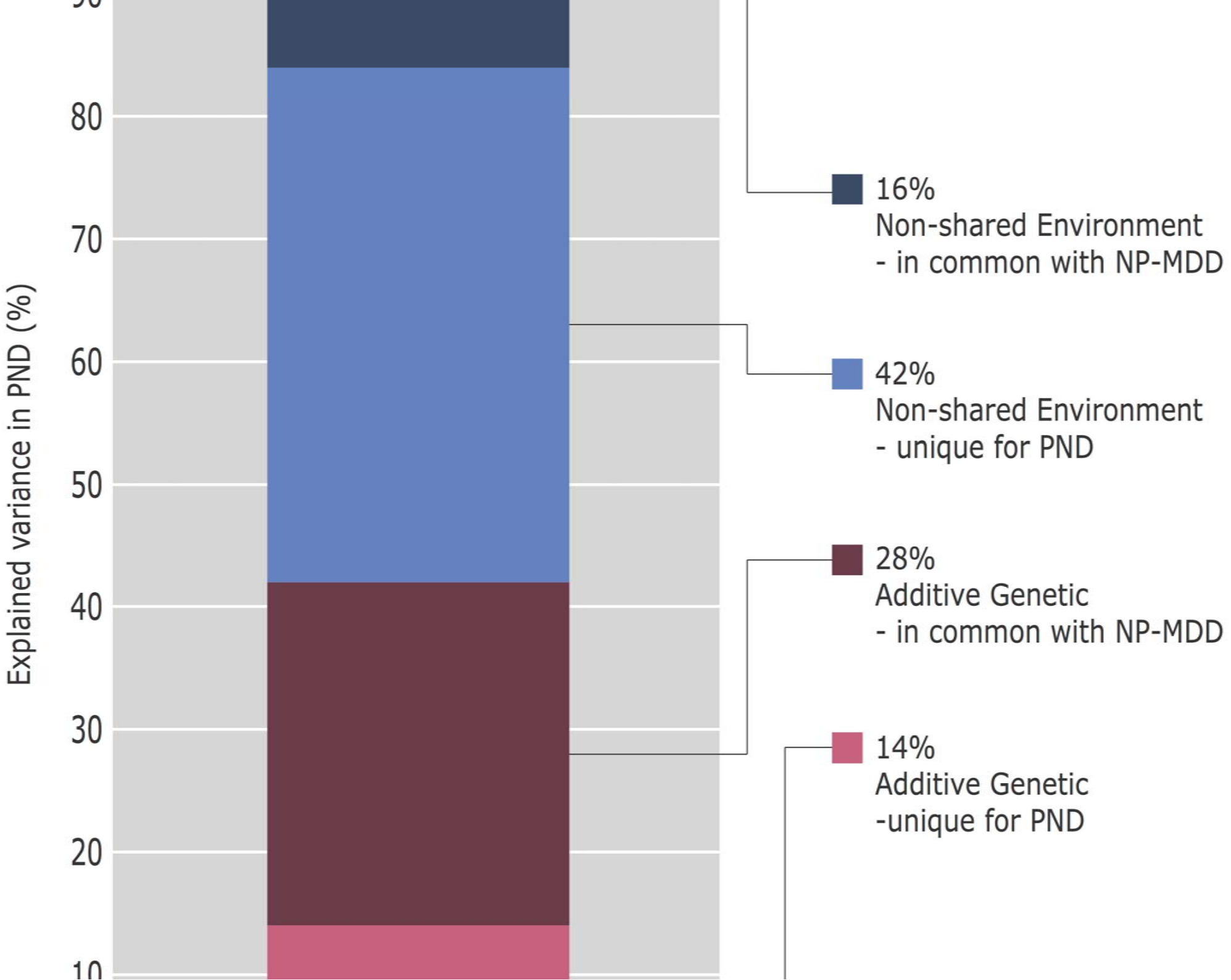
* Register based data on hospital admissions for depression was used to define antenatal depression (during pregnancy) and postnatal depression (within 12 months postpartum) (see Methods).

[a] Wald type confidence intervals, standard error calculated using the delta method.

[b] An AE model, were the C parameter was fixed at zero, was considered as the estimate of C was zero in the ACE model.

[c] Problems with standard error estimates. No standard errors were obtained.

[d] Number of pairs consisting of two individuals positive for the disorder.


Explained variance in PND (%)
90
80
70
60
50
40
30
20
10
16%
Non-shared Environment
- in common with NP-MDD
42%
Non-shared Environment
- unique for PND
28%
Additive Genetic
- in common with NP-MDD
14%
Additive Genetic
-unique for PND